Effect of -3 Polyunsaturated Fatty Acids in Young People at Ultrahigh Risk for Psychotic Disorders: The NEURAPRO Randomized Clinical Trial

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Abstract: Importance A promising treatment to prevent onset and improve outcomes in patients at ultrahigh risk for psychosis is dietary supplementation with long-chain -3 polyunsaturated fatty acids (PUFAs). Objective To determine whether treatment with -3 PUFAs in combination with a high-quality psychosocial intervention (cognitive behavioral case management [CBCM]) is more effective than placebo plus CBCM. Design, Setting, and Participants NEURAPRO, a double-blind, placebo-controlled, randomized clinical trial, was conducted from March 1, 2010, to September 30, 2014, in 10 specialized early psychosis treatment services in Australia, Asia, and Europe. The primary analysis used the intention-to-treat approach. Interventions A daily dose of 1.4 g of -3 PUFAs or placebo (paraffin oil), plus 20 or fewer sessions of CBCM over the 6-month study period. Main Outcomes and Measures The primary outcome was transition to psychosis status at 6 months. The secondary outcomes were general levels of psychopathology and functioning, as assessed by the Brief Psychiatric Rating Scale (BPRS) (range, 24-168), Scale for the Assessment of Negative Symptoms (SANS) (range, 0-125), Montgomery-Åsberg Depression Rating Scale (MADRS) (range, 0-60), Young Mania Rating Scale (YMRS) (range, 0-44), Social and Occupational Functioning Assessment Scale (SOFAS) (range, 0-100), and the Global Functioning: Social and Role scale (range, 0-10). For SOFAS and Global Functioning: Social and Role scale, higher scores were better; for other measures, lower scores were better. Results In this study of 304 adults at ultrahigh risk for psychotic disorders, 153 (50.3%) received -3 PUFAs and 151 (49.7%) received placebo. In all, 139 (45.7%) were male; mean (SD) age was 19.1 (4.6) years. The Kaplan-Meier-estimated 6-month transition rates were 5.1% (95% CI, 1.3%-8.7%) in the control group and 6.7% (95% CI, 2.3%-10.8%) in the -3 PUFA group. At 12 months, the rates were 11.2% (95% CI, 5.5%-16.7%) in the control group and 11.5% (95% CI, 5.8%-16.9%) in the -3 PUFA group. No significant difference was observed between the transition rates of both groups (hazard ratio, 1.1; 95% CI, 0.55-2.23; P = .76, stratified log-rank test). Conclusions and Relevance This trial clearly failed to replicate the findings of the original single-center trial. The most likely explanation is that -3 PUFAs lack efficacy under these conditions. However, the lower-than-expected transition rate may have prevented a test of the main hypothesis. Given the substantial symptomatic and functional improvement in both groups, the other treatments received (ie, CBCM and antidepressants) likely produced a ceiling effect beyond which -3 PUFAs, even if effective, could not be shown to confer additional benefits. Nevertheless, the main conclusion is that -3 PUFAs are not effective under conditions where good quality, evidence-based psychosocial treatment is available. Trial Registration anzctr.org.au Identifier: 12608000475347.

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Effect of ω-3 Polyunsaturated Fatty Acids in Young People at Ultrahigh Risk for Psychotic Disorders
The NEURAPRO Randomized Clinical Trial

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IMPORTANCE A promising treatment to prevent onset and improve outcomes in patients at ultrahigh risk for psychosis is dietary supplementation with long-chain ω-3 polyunsaturated fatty acids (PUFAs).

OBJECTIVE To determine whether treatment with ω-3 PUFAs in combination with a high-quality psychosocial intervention (cognitive behavioral case management [CBCM]) is more effective than placebo plus CBCM.

DESIGN, SETTING, AND PARTICIPANTS NEURAPRO, a double-blind, placebo-controlled, randomized clinical trial, was conducted from March 1, 2010, to September 30, 2014, in 10 specialized early psychosis treatment services in Australia, Asia, and Europe. The primary analysis used the intention-to-treat approach.

INTERVENTIONS A daily dose of 1.4 g of ω-3 PUFAs or placebo (paraffin oil), plus 20 or fewer sessions of CBCM over the 6-month study period.

MAIN OUTCOMES AND MEASURES The primary outcome was transition to psychosis status at 6 months. The secondary outcomes were general levels of psychopathology and functioning, as assessed by the Brief Psychiatric Rating Scale (BPRS) (range, 24-168), Scale for the Assessment of Negative Symptoms (SANS) (range, 0-125), Montgomery-Åsberg Depression Rating Scale (MADRS) (range, 0-60), Young Mania Rating Scale (YMRS) (range, 0-44), Social and Occupational Functioning Assessment Scale (SOFAS) (range, 0-100), and the Global Functioning: Social and Role scale (range, 0-10). For SOFAS and Global Functioning: Social and Role scale, higher scores were better; for other measures, lower scores were better.

RESULTS In this study of 304 adults at ultrahigh risk for psychotic disorders, 153 (50.3%) received ω-3 PUFAs and 151 (49.7%) received placebo. In all, 139 (45.7%) were male; mean (SD) age was 19.1 (4.6) years. The Kaplan-Meier–estimated 6-month transition rates were 5.1% (95% CI, 1.3%-8.7%) in the control group and 6.7% (95% CI, 2.3%-10.8%) in the ω-3 PUFA group. At 12 months, the rates were 11.2% (95% CI, 5.5%-16.7%) in the control group and 11.5% (95% CI, 5.8%-16.9%) in the ω-3 PUFA group. No significant difference was observed between the transition rates of both groups (hazard ratio, 1.1; 95% CI, 0.55-2.23; $P = .76$, stratified log-rank test).

CONCLUSIONS AND RELEVANCE This trial clearly failed to replicate the findings of the original single-center trial. The most likely explanation is that ω-3 PUFAs lack efficacy under these conditions. However, the lower-than-expected transition rate may have prevented a test of the main hypothesis. Given the substantial symptomatic and functional improvement in both groups, the other treatments received (ie, CBCM and antidepressants) likely produced a ceiling effect beyond which ω-3 PUFAs, even if effective, could not be shown to confer additional benefits. Nevertheless, the main conclusion is that ω-3 PUFAs are not effective under conditions where good quality, evidence-based psychosocial treatment is available.

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Supplemental content

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Psychotic illnesses typically emerge from initially subtle and relatively nonspecific symptoms, building through a prodromal period of subthreshold positive symptoms to cross a somewhat arbitrary threshold that enables a first episode of psychosis to be diagnosed.[1] The operational definition of the ultrahigh risk (UHR) mental state,[2,3] which prospectively identifies people at incipient risk of progression to full-threshold psychosis, has catalyzed an intense research effort as well as significant reforms to clinical care.[4,5] The validation of the UHR criteria has enabled the study of a range of treatment strategies to relieve distress, improve functioning, and reduce the risk for progression to a psychotic illness.[2,3,6-14]

Eleven trials assessing psychosocial or pharmacologic interventions, alone or in combination, have been carried out in UHR cohorts. A recent meta-analysis has shown that these interventions are effective, resulting in an overall risk reduction of 54% at 12 months with a number needed to treat of 8 (range, 4-13).[15] All treatments appeared to reduce the risk during the first 6 to 12 months. In line with the clinical staging model of illness,[16-20] during the earliest stage of illness, safer interventions, such as long-chain ω-3 polyunsaturated fatty acids (PUFAs) and cognitive behavioral therapy (CBT), should be regarded as the preferred options for first-line treatment. Cognitive behavioral therapy, a well-established and safe psychosocial intervention adapted for this stage of illness, has been found to be effective in many, although not all, of the published trials.[21-26] However, the most striking result to date was the finding that ω-3 PUFAs were superior to placebo in reducing the risk for transition to psychosis and psychiatric morbidity in general, not only during the period of treatment, but also for a subsequently prolonged time (median, 6.7 years).[27,28] Safe and beneficial to health in many ways, ω-3 PUFAs represent a simple and relatively inexpensive potential treatment strategy. The initial ω-3 PUFAs study[27] was therefore clearly worthy of attempted replication.

Key Points

Question Are ω-3 polyunsaturated fatty acids (ω-3 PUFAs) effective in reducing transition to psychosis in young people at ultrahigh risk for psychotic disorders on a background of psychosocial and other care?

Findings In a multicenter, randomized clinical trial of 304 patients, no evidence of efficacy for ω-3 PUFAs was found. Outcomes were equally positive in both the ω-3 PUFA and placebo groups, with low transition rates and overall symptomatic functional improvement.

Meaning Use of ω-3 PUFAs is not effective under conditions in which evidence-based and good-quality psychosocial treatment are available.

Methods

Study Design and Setting

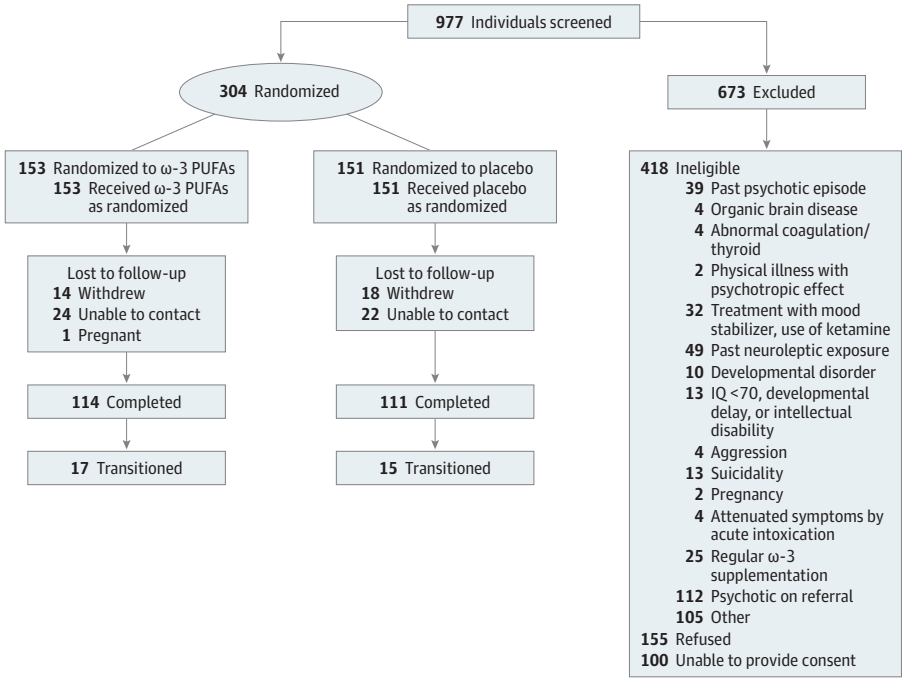
NEURAPRO was a double-blind, placebo-controlled, randomized clinical trial of ω-3 PUFA therapy given for 6 months, followed by an additional 6-month follow-up period, in 304 participants who received either ω-3 PUFAs together with cognitive behavioral case management (CBCM) or placebo with CBCM. The total study period was 12 months from March 1, 2010, to September 30, 2014. Assessments were made at baseline, 6, and 12 months after entry. In addition, assessments of psychopathology were conducted monthly during the first 6 months and also at month 9. The 6- and 12-month results are reported herein. The study was performed in accordance with the Declaration of Helsinki[29] and is consistent with International Council for Harmonisation of Good Clinical Practice.[30] The National Health and Medical Research Council of Australia National Statement on Human Research was also adhered to, appropriate ethical approval was obtained by each site (Melbourne, Australia: Melbourne Health Research Ethics Committee; Sydney, Australia: Sydney South West Area Health Service Ethics Review Committee; Basel, Switzerland: Ethics Commission for Basel; Zurich, Switzerland: Cantonal Ethics Commission Zurich; Jena, Germany: University Clinic Jena Ethics Commission; Copenhagen, Denmark: Capital Region Research Ethics Committee; Hong Kong: Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster; Vienna, Austria: Medical University of Vienna Ethics Commission; Singapore: National Healthcare Group Domain Specific Review Board; and Amsterdam, the Netherlands: Academic Medical Centre Medical Ethics Committee), and any local regulatory requirements were met before the trial commenced. Written informed consent was obtained; for those younger than 17 years, parental or guardian consent was sought. Participants received financial compensation. Complete details on the study methodology are reported by Markulev et al,[31] and the trial protocol is available in Supplement 1.

Help-seeking individuals attending trial centers were eligible to participate if they were aged 13 to 40 years and met the UHR criteria. In a variation to the previous UHR intervention studies, all participants either had a low level of functioning (Social and Occupational Functioning Assessment Scale [SOFAS] scores <50) sustained for at least a year or had experienced a significant decrease in their functioning (≥30% reduction in their SOFAS score) over the past year.[32] Exclusion criteria included a previous psychotic episode of 7 days or longer, current symptoms due to acute intoxication, organic brain disease, serious developmental disorder, abnormal coagulation profile or thyroid function, physical illness with a psychotropic effect, current treatment with mood stabilizers, past neuroleptic exposure to a total lifetime haloperidol equivalent dose of more than 50 mg, IQ of less than 70, dangerous behavior, aggression or suicidality, pregnancy, or current supplementation with ω-3 PUFA.[31]

Randomization

Participants were randomized at study entry to either the ω-3 PUFA plus CBCM group, or the placebo plus CBCM group via an online electronic data management system (**Figure 1**). Randomization was stratified by site and total score on the Montgomery-Åsberg Depression Rating Scale (MADRS) (total score

Figure 1. CONSORT Diagram of Participant Distribution



Randomization was stratified by site and Montgomery-Åsberg Depression Rating Scale score (<21 and ≥21; higher scores indicate worse symptoms). Adherence rates were 43.1% for the ω-3 polyunsaturated fatty acids (ω-3 PUFAs) group and 41.1% for the placebo group.

range, 0-60, with the lowest score indicating the best level)[33] since both depression and antidepressants may affect UHR symptoms and illness progression.[34-37] All participants and clinicians involved in delivering interventions, assessing outcomes, and data entry were blind to group assignment. The trial statistician (H.P.Y.) was unblinded at the analysis stage.

Study Interventions

Participants received either ω-3 PUFAs or placebo together with clinical care with up to 20 sessions of CBCM for the 6-month intervention phase, after which administration of both the ω-3 PUFAs and placebo were ceased, although patients could continue to access CBCM on the basis of need throughout this 6-month follow-up.[31] A total of 125 participants (41.1%) continued to receive CBCM after the 6-month follow-up visit, with a mean (SD) of 4.1 (3.7) (range, 1-16) sessions attended.

For the first 12 months of the study, therapy with selective serotonin reuptake inhibitors was permitted for treatment of moderate to severe major depression (MADRS score ≥21 for at least 2 consecutive weeks), and benzodiazepine therapy was permitted for anxiety. The use of antipsychotics or mood stabilizers was not permitted at any time during the trial unless a participant was withdrawn from the study before 12 months and these treatments were deemed necessary according to clinical guidelines.

The study medication comprised a daily dose of 4 gelatin capsules throughout the 6-month treatment period. Participants were dispensed bottles of capsules, with each capsule containing either (1) 0.65 to 0.75 g of concentrated marine fish oil (active intervention: 840 mg of eicosapentaenoic acid and 560 mg of docosahexaenoic acid or approximately 1.4 g of ω-3 PUFAs per day) or (2) 0.65 to 0.75 g of paraffin oil (placebo intervention). This dose was similar to that in the previous study.[27]

Outcome Measures

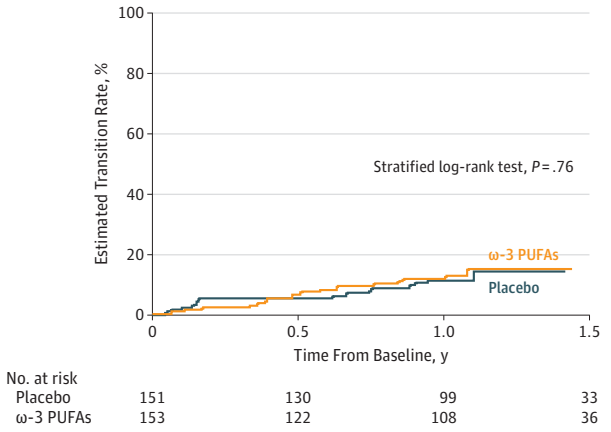
The primary outcome was transition to psychosis status at 6 months, with transition defined on the basis of operationalized criteria and assessed with the Comprehensive Assessment of the At-Risk Mental State.[32] Diagnoses (both psychotic and nonpsychotic) were determined with the *Structured Clinical Interview for* DSM-IV-TR *Axis I Disorders*,[38] and the secondary measures included the Brief Psychiatric Rating Scale (BPRS) (total score range, 24-168),[39] Scale for the Assessment of Negative Symptoms (SANS) (total score range, 0-125),[40] MADRS,[33] Young Mania Rating Scale (YMRS) (total score range, 0-44),[41] SOFAS (total score range, 0-100),[42] and the Global Functioning: Social and Role scales (total score range, 0-10).[43] For SOFAS and Global Functioning: Social and Role scale, the higher the score the better; for the other measures, the lower the score the better.

Adherence to the study medication was assessed monthly for each participant based on capsule count. The mean adherence rating over the 6-month intervention period was then computed and categorized as either adherent (≤25% of capsules returned) or nonadherent (>25% of capsules returned). Adverse events and serious adverse events were monitored throughout the study and were assessed at each visit during the intervention phase and classified into categories for further analysis.

Statistical Analysis

The study was powered to detect a 13% difference in the transition rates between the 2 treatment groups, with the 6-month

Figure 2. Survival Curves of the Rate of Transition to Psychosis in the ω-3 Polyunsaturated Fatty Acid (ω-3 PUFA) and Placebo Groups



transition rate in the placebo group assumed to be 15%.[31] The primary analysis used the intention-to-treat approach and compared the difference in transition rates between the treatment groups using survival analysis with the stratified log-rank test and Cox regression analysis with recruitment site and baseline MADRS score (<21 and ≥21) used as stratifying factors. General linear modeling and linear mixed-effects model analysis were used to compare the secondary outcomes (symptoms and functioning) for the 2 groups. Further analysis to compare the treatments was conducted by taking adherence into account for both the primary and secondary outcomes.

Risk class analysis was also undertaken using demographic characteristics (age, sex, race, years of education, and duration of untreated symptoms) and symptom and functioning measures (BPRS, SANS, MADRS, YMRS, SOFAS, and Global Functioning: Social and Role) as potential risk factors to identify a subgroup of patients who might be at a relatively higher risk of transition. The 2 treatments were then compared within this subgroup in terms of the primary and secondary outcomes using the above-mentioned statistical methods. Significance was set at $P = .05$. Data analysis was conducted using SPSS, version 22I (BM Corp) and S-PLUS, version 6.1 (Insightful Corp).

Results

Study Sample

The study cohort consisted of 304 individuals, with 153 persons randomly assigned to ω-3 PUFA treatment (50.3%) and 151 to placebo (49.7%). The baseline characteristics of both groups were similar (eTables 1 and 2 in Supplement 2). Fourteen of the 153 participants (9.2%) from the ω-3 PUFA group and 18 of 151 individuals (11.9%) from the placebo group discontinued the intervention prematurely (ie, <6 months). Twenty-four (15.7%) participants from the ω-3 PUFA group were unable to be contacted and 1 person (0.6%) became pregnant, and 22 (14.6%) participants from the placebo group were unable to be contacted. Thus, a total of 79 participants (26.0%) were lost to follow-up (Figure 1). The mean (SD) duration of untreated illness was 891.1 (969.1) days (median, 467 days) in the ω-3 group and 897.6 (115.6) days (median, 431.5 days) in the placebo group.

Efficacy

Primary Outcome Measure

The stratified log-rank test indicated no significant difference between ω-3 PUFAs and placebo in transition rate ($P = .76$). The Kaplan-Meier–estimated 6-month transition rates were 5.1% (95% CI, 1.3%-8.7%) in the control group and 6.7% (95% CI, 2.3%-10.8%) in the ω-3 PUFA group. At 12 months, the transition rates were 11.2% (95% CI, 5.5%-16.7%) in the control group and 11.5% (95% CI, 5.8%-16.9%) in the ω-3 PUFA group (**Figure 2**). Cox regression analysis, again stratified for recruitment site and baseline MADRS score, also showed no significant difference between the 2 groups (hazard ratio [HR], 1.1; 95% CI, 0.55-2.23; $P = .76$).

Secondary Outcome Measures

General linear model analysis, with an a priori significance threshold of $P < .05$ and no adjustment for multiple testing, was used to compare treatments on changes in symptom and functioning measures between baseline and the 6- and 12-month follow-up visits. Two measures showed an almost significant improvement at month 6: the MADRS ($P = .09$) and the SOFAS ($P = .07$), and a statistically significant improvement was seen on the Global Functioning: Social and Role scale ($P = .02$). However, the direction of these changes was in favor of the placebo group. No statistically significant difference was seen between the groups in any of the measures at month 12 (**Table**). Linear mixed-effects modeling was used to compare the 2 treatments in the rate of improvement over time for each of the symptom and functioning measures. Although there was a significant improvement over time for each measure, the rate of improvement did not significantly differ between ω-3 PUFAs and placebo on any of the measures (Table).

Adverse Events

Adverse events were assessed at baseline and monthly during the intervention phase, and then at the 6- and 12-month follow-up visits. A number of adverse events were recorded in both groups. The incidence rates ranged from less than 1% (increased bleeding) to about 30% (gastrointestinal problems). No adverse events were regarded as serious adverse events related to study medication (eTable 3 in Supplement 2).

Adherence and Concomitant Medication

There were 66 adherent participants (43.1%) in the ω-3 PUFA group and 62 in the placebo group (41.1%). However, a total of 83 participants had missing data for the capsule counts (ω-3 PUFA, 35; placebo, 48), 9 of whom (10.8%) transitioned to psychosis. To avoid losing participants from the analysis, these 83 individuals were assumed to be nonadherent. **Figure 3** shows the survival curves comparing the 2 groups for the adherent and nonadherent participants. As expected, the transition rate was lower in the adherent participants; however,

Table. General Linear Model Analysis Comparing the Placebo and ω-3 PUFA Groups[a]

Characteristic[b]	General Linear Model Analysis				Linear Mixed-Effects Model Analysis		
	Month 6 Minus Baseline		Month 12 Minus Baseline				
	Mean (SD)	*P* Value[c]	Mean (SD)	*P* Value[c]	*P* Value[d]	Overall Estimated Rate of Change (SE)	*P* Value[e]
Brief Psychiatric Rating Scale							
Total							
Placebo	−7.4 (8.5)	.36	−7.8 (8.4)	.10	.48	−0.02 (0.0015)	<.001
ω-3 PUFAs	−7.3 (8.5)		−7.8 (9.3)				
Psychotic subscale							
Placebo	−2.4 (3.2)	.85	−2.5 (3.3)	.66	.91	−0.006 (0.0005)	<.001
ω-3 PUFAs	−2.3 (2.5)		−2.3 (3.1)				
Scale for the Assessment of Negative Symptoms							
Total							
Placebo	−6.5 (11.7)	.14	−6.2 (11.7)	.89	.82	−0.018 (0.0020)	<.001
ω-3 PUFAs	−5.9 (9.6)		−7.5 (11.7)				
Affective flattening or blunting							
Placebo	−1.8 (4.6)	.24	−1.4 (4.8)	.89	.49	−0.005 (0.0008)	<.001
ω-3 PUFAs	−1.9 (4.0)		−2.2 (4.8)				
Alogia							
Placebo	−0.8 (2.6)	.14	−0.6 (2.4)	.60	.62	−0.002 (0.0004)	<.001
ω-3 PUFAs	−0.8 (2.4)		−1.1 (2.5)				
Avolition-apathy							
Placebo	−1.4 (3.0)	.45	−1.5 (3.4)	.72	.60	−0.004 (0.0005)	<.001
ω-3 PUFAs	−1.3 (2.8)		−1.7 (2.9)				
Anhedonia-asociality							
Placebo	−2.1 (4.0)	.40	−2.3 (4.3)	.80	.59	−0.005 (0.0007)	<.001
ω-3 PUFAs	−1.7 (3.5)		−2.0 (4.3)				
Attention							
Placebo	−0.4 (1.4)	.22	−0.3 (1.5)	.20	.92	−0.001 (0.0003)	<.001
ω-3 PUFAs	−0.3 (1.8)		−0.7 (1.8)				
Young Mania Rating Scale							
Total							
Placebo	−1.1 (3.0)	.24	−0.9 (2.6)	.61	.70	−0.002 (0.0005)	<.001
ω-3 PUFAs	−0.9 (3.1)		−0.8 (3.1)				
Montgomery-Åsberg Depression Rating Scale							
Total							
Placebo	−9.3 (8.4)	.09	−9.0 (−9.6)	.72	.79	−0.020 (0.0016)	<.001
ω-3 PUFAs	−7.9 (8.7)		−9.6 (−9.4)				
Social and Occupational Functioning Assessment Scale							
Placebo	12.6 (14.9)	.07	14.3 (16.8)	.95	.36	0.036 (0.0030)	<.001
ω-3 PUFAs	8.9 (16.5)		14.7 (19.1)				
Global Functioning							
Social							
Placebo	0.6 (1.4)	.45	0.7 (1.6)	.47	.41	0.002 (0.0003)	<.001
ω-3 PUFAs	0.5 (1.2)		0.5 (1.4)				
Role							
Placebo	0.9 (1.6)	.02	1.0 (2.0)	.78	.63	0.002 (0.003)	<.001
ω-3 PUFAs	0.5 (1.7)		0.9 (1.7)				

Abbreviation: ω-3 PUFAs, ω-3 polyunsaturated fatty acids.

[a] Change between baseline and follow-up (months 6 and 12) and linear mixed-model analysis comparing the 2 treatments for rate of change over time.

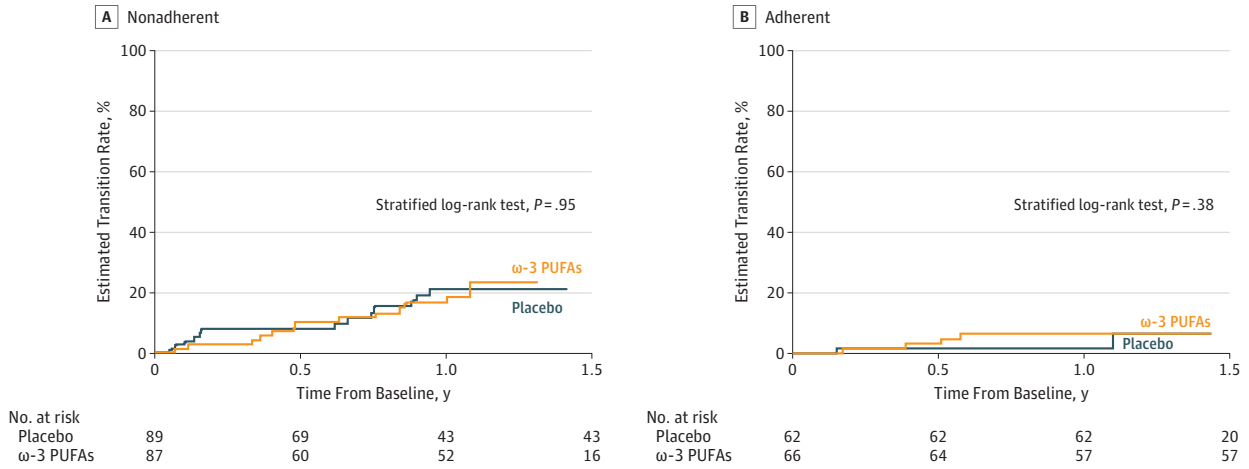
[b] For the Brief Psychiatric Rating Scale, score range is 24 to 168; lowest score indicates the best level.[39] For the Scale for the Assessment of Negative Symptoms, score range is 0 to 125; lowest score indicates the best level.[40] For the Young Mania Rating Scale, score range is 0-44; lowest score indicates the best level.[41] For the Montgomery-Åsberg Depression Rating Scale, score range is 0-60; lowest score indicates the best level).[33] For the Social and Occupational Functioning Assessment Scale, score range is 0-100; higher scores are better.[42] For the Global Functioning: Social and Role scales, score range is 0-10; higher scores are better.[43]

[c] Placebo vs ω-3 PUFA groups for change at month 6 to 12 vs baseline.

[d] Placebo vs ω-3 groups for improvement from baseline to month 12.

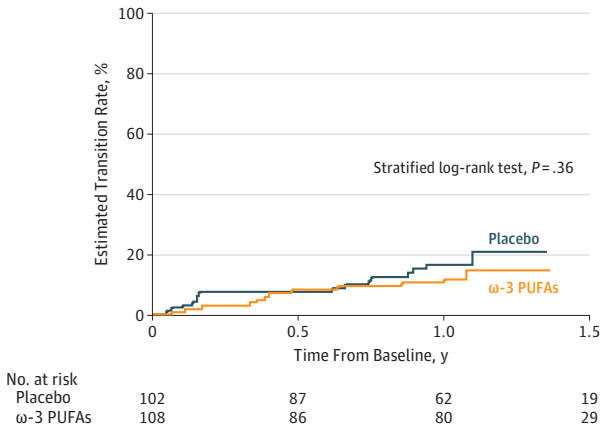
[e] Overall estimated rate of change.

Figure 3. Survival Curves for the Rate of Transition in the ω-3 Polyunsaturated Fatty Acid (ω-3 PUFA) and Placebo Groups Based on Adherence Status



A, A total of 176 participants were nonadherent. B, A total of 128 participants were adherent.

Figure 4. Survival Curves for the Rate of Transition in Ultrahigh-Risk Participants



Ultrahigh risk was considered a Baseline Montgomery-Åsberg Depression Rating Scale score of 14 or higher.

stratified log-rank tests comparing the 2 treatment groups showed that there was no significant difference between them regardless of adherence status (adherent, $P = .38$; nonadherent, $P = .95$) (Figure 3).

The symptom and functioning measures were further analyzed by taking adherence into account, again using general linear modeling and a linear mixed-effects model. Again, no significant difference between the 2 treatment groups was found ($P > .14$ for all measures), regardless of adherence status.

The mean (SD) number of CBCM sessions attended was 11.2 (6.4) for the ω-3 PUFA group and 10.3 (6.0) for the placebo group. The overall median number of CBCM sessions attended was 8 (range, 1-35). Again, stratified log-rank tests showed that there was no significant difference between the treatment groups in terms of transition rate for those with a number of CBCM sessions equal to or below the median ($P = .31$), as well as for those above the median ($P = .50$). Concomitant medication use after randomization included antidepressants in 98 (64.1%) of those in the ω-3 PUFA group and 91 (60.3%) of those in the placebo group ($P = .57$) and anxiolytics in 32 (20.9%) of the participants in the ω-3 PUFA group and 44 (29.1%) of those in the placebo group ($P = .13$).

Risk Class Analysis

Risk class analysis was undertaken in an effort to identify participants at the highest risk of transition to assess the effectiveness of ω-3 PUFA in this subgroup. Demographic characteristics and symptom and functioning measures were used as potential risk factors and their significance on transition rate was determined using Cox regression analysis in the placebo group to remove any potential intervention effect. The only measures found to be significant were BPRS total score (HR, 1.07; 95% CI, 1.01-1.13; $P = .03$) and MADRS total score (HR, 1.09; 95% CI, 1.02-1.18; $P = .009$). Because these 2 measures were highly correlated (Pearson correlation, 0.67), the MADRS score was chosen as the stratifying factor for this analysis since it had a lower P value, had no missing values, and was 1 of the stratifying variables for the randomization. A cutoff score of 14 for the MADRS was found to correspond to the most significant P value ($P = .001$). This score was considered valid because participants in the placebo group who had a MADRS total score lower than 14 had an estimated 1-year transition rate of 0%, whereas those with a score of 14 or higher had an estimated 1-year transition rate of 16.5%. However, when the transition rates of the 2 treatment groups were compared within the high-risk (ie, those with a MADRS score ≥14) cohort, no significant difference was found (**Figure 4**).

Discussion

To our knowledge, this is the first randomized, placebo-controlled, multicenter clinical trial to test the efficacy of long-chain ω-3 PUFAs in preventing transition to psychosis in young

people at UHR for psychosis. Although ω-3 PUFAs were well tolerated, they did not demonstrate an advantage over placebo in the prevention of psychosis at 6- or 12-month follow-up evaluations. Secondary outcome measures of psychiatric symptoms and functioning tended to favor the placebo group. This outcome is difficult to explain other than as a chance finding. The results represent a clear failure to replicate the earlier single-center trial.[27,28]

Although the obvious and most likely explanation for this nonreplication is that ω-3 PUFA supplementation is not effective for preventing the onset of psychosis, it remains at least possible that other explanations may have been responsible. The 12-month transition rate of 10.5% was lower than expected and below the rate of 16.1% seen in the previous single-center trial.[27] There are 2 possible explanations for this lower transition rate. First, the manualized CBCM intervention and the high level of antidepressant treatment received by both treatment groups in the present study may have been sufficiently effective to have produced a ceiling effect beyond which there was no scope for ω-3 PUFAs to confer additional benefit. If so, the main hypothesis may not have been testable. In support of this possibility is the fact that the placebo group in the original trial failed to show the level of symptomatic and functional improvement seen in the present study.[44] Second, the sample may have been insufficiently enriched for risk of transition. At first glance the low transition rate might be regarded as having reduced the power of the study to detect an effect; however, since there was no indication of efficacy of the ω-3 PUFAs, more power through a larger sample size would not have helped. It remains possible that ω-3 PUFAs may be beneficial in the absence of other treatments or possibly in a subsample of cases. Longer-term follow-up, subgroup analysis, and additional studies may clarify these issues.

Lower transition rates have been observed over the past decade and several possible explanations have been considered.[45-48] These explanations include reduced duration of symptoms and lesser initial severity and enrichment, yet we found no evidence for this in the present study. Many trials have shown that CBT is effective in delaying and reducing transition,[15] and in contrast to the original study,[27] all patients in the present study received substantial levels of high-quality CBT-based intervention. In addition, the high proportion of participants who received antidepressant medication (62% vs 10% in the original study) may also have contributed to the low overall transition rate and better dimensional outcomes. Previous studies have suggested an effect of antidepressant medication in decreasing that transition rate in UHR samples.[34-37] In the present study, antidepressant medication was prescribed for participants who were more symptomatic and depressed, and who therefore were at higher risk of transition to psychosis, thus potentially having a selectively greater effect on reducing the overall transition rate.

Strengths of the study include the randomized, placebo-controlled design, the use of standardized inclusion and exit criteria, interrater reliability testing, the monitoring of treatment adherence, and the confirmation at 12-month follow-up by means of standardized interview and case review that all people who met the exit criteria had made transitions to genuine psychotic disorders.

Limitations

A limitation of this study is that the use of nonstudy ω-3 PUFA supplements cannot be excluded and the test agent may thus be present in both the treatment and control groups.[49] Nonstudy ω-3 PUFA intake may have decreased the difference in ω-3 PUFA status between the groups, since both awareness of the potential health benefits and availability of ω-3 PUFAs has increased over the past decade.

Therapeutic effects of ω-3 PUFAs may be present in subgroups characterized by certain biological or phenotypic markers[28] that can be considered as moderators of clinical response.[50] These supplements are specifically effective in subgroups of depression characterized by high levels of inflammation.[51] Subgroup analyses using baseline membrane fatty acid levels and inflammatory markers are planned. We are also investigating whether biological measures of ω-3 PUFA intake that accurately define adherence to study medication, as well as nonstudy intake, such as changes in erythrocyte membrane fatty acid levels, will provide a clearer view of whether ω-3 PUFAs showed any benefit in subgroups of this cohort.

Conclusions

This trial has failed to replicate the findings of a previous single-center study.[27] Other multicenter trials, ongoing analysis of the data from the present study, and future research will help to ultimately determine whether ω-3 PUFAs have a role in the reduction of risk and early treatment of psychotic disorder.

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